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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Behavioral data was collected using ANYMaze v4.75 (Stoelting). Microscopy data was collected using LAS AF software v3.7.4 (Leica). Electrophysiological data was collected using DigiData v10.5.2.6 (Molecular Devices).
Data analysis	Behavioral data was analyzed using ANYMaze v4.75 (Stoelting). Imaging data was analyzed using ImageJ-Fiji v1.0 (NIH) and Neurolucida 360 v2020 (MBF Bioscience). Electrophysiological data was analyzed using pClamp v10.7.0.3 (Molecular Devices) and Minianalysis v6.0.7 (Synpatosoft). Statistical analysis was performed using Prism v7.0 (Graphpad).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

No datasets were generated or analyzed during the current study. Source data for all figures are provided with the paper.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No statistical methods were used to pre-determine sample size, but the sample sizes matched or exceeded those previously reported in the literature to detect behavioral, electrophysiological, and morphological changes in Rett syndrome mice (Samaco et al., 2013; Lu et al., 2016).
Data exclusions	No data were excluded from the analysis
Replication	Each experiment was replicated at least two times. For all experiments, all attempts at replication were successful.
Randomization	Mice were divided randomly into experimental cohorts. All mice were housed with genotypes intermixed.
Blinding	Data collection and analysis was performed blinded to genotype. Genotyping was performed after data acquisition and analysis.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Primary antibodies: cFos (Millipore, Cat# ABE457), MeCP2 (Cell Signaling Technologies, Cat# 3456), NeuN (Millipore, Cat# MAB377). Secondary antibodies: Alexa Fluor 488 (Thermo Fisher, Cat# A-11001), Alexa Fluor 647 (Thermo Fischer, Cat# A-21244), and Streptavidin Alexa Fluor 488 (Thermo Fischer, Cat# S32354).
Validation	All antibodies are commercially available and validated for immunofluorescence in rodent tissue according to the manufacturer's website. For cFos, "a representative lot detected c-Fos in the rat pons and rat cerebellum tissues. For MeCP2, the antibody was validated "in the presence of a control peptide and antigen-specific peptide." For NeuN, the antibody "reacts with most neuronal cell types throughout the nervous system of mice."

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Male and female mice were used for breeding, but only female mice were used for behavioral experiments. Strains: B6.129P2(C)-Mecp2tm1.1Bird/J (Mecp2-; JAX stock: 003890), Fostm2.1(iCreERT2)Luo/J (Fos2A-iCreER; JAX stock: 030323), B6;129S6-Tg(Camk2a-cre/ERT2)/1Aibs/J (Camk2aCreER; JAX stock: 012362), B6.Cg-Gt(ROSA)26Sortm14(CAG-tdTomato)Hze/J (Ai14; JAX stock: 007914), and B6;129S4-Gt(ROSA)26Sortm9(EGFP/Rpl10a)Amc/J (EGFP-L10a; JAX stock: 024750). All mice were maintained on a C57BL/6J background. Age for behavioral analysis: 8-24 weeks (rotarod training), 4-12 weeks (Morris water maze training). Age for histological and electrophysiological analysis: 13 weeks.
Wild animals	The study did not involve wild animals
Field-collected samples	The study did not involve samples collected from the field

Ethics oversight	All procedures were performed in accordance with the Institution Animal Care and Use Committee at Baylor College of Medicine.

Note that full information on the approval of the study protocol must also be provided in the manuscript.